INFECTIONS OF THE BILIARY TRACT, WITH SPECIAL REFERENCE TO LATENT (OR MASKED) AND TYPHOID INFECTIONS.[1]

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THAT infections of the biliary tract are by no means uncommon has long been recognized. The gross and quite obvious manifestations of such infections—suppurative cholangitis, suppurative, phlegmonous, and gangrenous cholecystitis, certain forms of abscess of the liver, etc.— were well recognized and quite accurately described by our forefathers. That these disorders, however, by no means comprise the totality of biliary infections has been demonstrated only during recent years, and even now the full import of other less obvious infections is not as widely known nor as keenly appreciated as is desirable. There are much more subtle infections of the biliary tract—ill-understood, frequently overlooked, and commonly misinterpreted: infections that often give rise to no symptoms, at least no noteworthy symptoms, for many years, if at all; infections diverse in their pathological lesions, variable in their sequels, and often complex and aberrant in their clinical manifestations; indeed, of many the symptomatology has not yet been completely worked out.

The observations to which I invite your attention are based primarily upon a statistical study of the clinical and other phenomena of 216 patients operated upon by Dr. John B. Deaver at the German Hospital, Philadelphia, during the last six years (1900 to 1905 inclusive).[2] My personal work has comprised a study of the gall-bladders removed by Dr. Deaver; of the pathological lesions at the necropsy in some of the fatal cases and in other cases (from the medical as well as the surgical wards) in which operation was not done; of the pathological lesions at the operation on some of the patients;[3] and a bacteriological study begun at the time of operation in seventy of the cases, and at the necropsy in a few of the fatal cases. I had thought to add certain details of my clinical experience gained elsewhere, but I have finally determined, in this communication, to deal only with the German Hospital material.

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[1] Part I of the Mütter Lecture of the College of Physicians of Philadelphia, delivered December 1, 1905.

[2] It is with much pleasure that I here record my indebtedness to Dr. Deaver for his many courtesies in connection with the study. Not only has he afforded me opportunities to witness many of his operations, but he has also generously permitted me to make a statistical study of his case-histories. I am also indebted to Dr. James R. Freeland, one of the resident physicians at the German Hospital, for assistance in compiling the statistics.

[3] The living as contrasted with the dead pathology, as Dr. Deaver delights to call it.

The somewhat restricted aspects of the broader subject of infections of the biliary tract that I have elected to discuss with you may be divided more or less artificially into two parts: the one comprising the more immediate, the second the more remote consequences of biliary infection. In many cases, however, the one fades almost imperceptibly into the other, and no sharp line of demarcation can be drawn between them. In this, Part I, I shall ask your attention especially to the pathways of infections of the biliary tract and to latent (or masked) and typhoid infections; in Part II, I shall discuss certain remote consequences of biliary infection, notably cholelithiasis, calculous cholecystitis, and adhesions of the upper abdomen, and I shall also direct your attention to the general principles of treatment and the indications for surgical intervention.

THE INFECTIOUS AGENTS.

The bacteriology of infections of the biliary tract has been studied by a large number of investigators—postmortem, at operation, and experimentally. Although considerable interest attaches to postmortem studies, the results are frequently vitiated by more or less obvious factors, and they cannot be relied upon implicitly unless the examinations are undertaken within a very short time after death. The conditions at operation, however, are quite different and the results much more trustworthy—although in subsiding or long-standing infections the primary infective agent may not be recovered, since it may have died out or have become overgrown by secondary invaders.

Although I have made some study of the bacteriology of the biliary tract at necropsies, these have been comparatively few and non-systematic, and they were undertaken largely because of special interest in individual, particularly typhoid fever, patients. At the German Hospital, however, we have studied the bacteriology of the biliary tract of seventy of the patients[1] operated upon by Dr. Deaver. The results are as follows:

	Cases.	Per cent.
Bacillus coli communis was found in	23	32.8
Bacillus typhosus was found in	7	10.0
Staphylococcus pyogenes aureus was found in	2	2.9
Streptococcus pyogenes was found in	1	1.4
Staphylococcus pyogenes albus was found in	1	1.4
Bacillus coli and Staphylococcus aureus were found in	2	2.9
No bacteria were found in	34	48.6

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[1] Fifty of these cases have already been reported by Dr. G. P. Müller, assistant pathologist to the German Hospital: The Pathology of Cholecystitis, Brooklyn Med. Journ., 1905, xix, 11

In general these results do not differ materially from those obtained by other observers, although the variety of bacteria is not as great as that of all other observers combined. Other bacteria isolated from the biliary tract comprise the cholera bacillus, Bacillus subtilis, Bacillus capsulatus aërogenes, leptothrix, etc. Biliary infections complicating pneumonia and influenza suggest the possibility of the pneumococcus and the influenza bacillus respectively being the etiological agent (general blood infection or a local infection from the duodenum), but as far as I know these organisms have not yet been isolated from the local lesions. In addition to the aforementioned bacteria I am inclined to attach some etiological importance to anaërobic bacteria—which abound in the intestine. I have long believed that these organisms play a not inconspicuous part in the etiology of appendicitis, and I am quite prepared to believe the same of infections of the biliary tract. A most suggestive study of this entire question has recently been published by Lippmann.[1]

THE PATHWAYS OF INFECTION.

The pathways whereby the biliary tract may become infected are several: (1) The diverticulum of Vater and the common bile duct; (2) the portal circulation; (3) the systemic circulation; (4) the lymphatic circulation; and (5) directly through the wall of the gall-bladder or the gall ducts from the peritoneum.

1. *Infection from the duodenum by way of the diverticulum of Vater and the common bile duct* has long been looked upon as at once the most likely and the most common source of biliary infections, but whether with good reason remains to be decided. Its possibility cannot be denied, its probability may be conceded, but the exact factors concerned in its mechanism have not yet been determined definitely. In this connection we have to bear in mind that although the frequency of Bacillus coli communis and of Bacillus typhosus in infections of the biliary tract suggests an intestinal source, these bacteria find a direct pathway from the intestine to the liver by way of the portal circulation. Furthermore, as a number of observers have pointed out, whereas the jejunum and the ileum always contain many bacteria, the duodenum when free from food is often bacteria-free; certainly, in health its bacterial-content is small and it does not contain the bacteria often found in cholangitis, cholecystitis, etc. It is quite conceivable, however, indeed it is quite likely, that in conditions of disease of the upper intestine when bacteria are present in the duodenum the biliary tract may become infected by way of the diverticulum of Vater;

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[1] Le microbisme biliaire normal et pathologique, Paris, 1904.

doubtless many of the cases of so-called catarrhal jaundice following gastroduodenitis arise in this fashion. But there are at least two important factors opposing a ready ascending infection of the biliary tract: The one, the action of the sphincter of the diverticulum, which has been estimated by Oggi[1] as exerting a force equal to a pressure within the common bile duct of 700 millimeters of water; the second, the influence of the free flow of bile. Indeed, it is doubtful whether infection of the biliary tract ever takes place by way of the diverticulum of Vater in the absence of stasis of the bile.

One of the most important, if not the most important, factor in preventing such infection is the free flow, that is the regular periodic expulsion, of the bile—the free flow of the bile rather than the bile itself, since we now know, contrary to former opinions, that the bile is a quite favorable medium for the growth of bacteria.

Assuming infection by way of the diverticulum of Vater, we must credit the invading bacteria with some degree of intelligence—else why in their onward march do they deviate to the left rather than to the right when they encounter the fork in the diverticulum? As far as we know the pancreatic duct is by no means as frequently infected as the biliary passages. The influence of differences in pressure in the two ducts cannot be of commanding importance, since in this event the secretion of the one would frequently be forced into the other. Should this be the common source of biliary infection we must also assume that in conditions of ordinary infection the pancreas and the liver are quite capable of dealing with the invading bacteria, and that it is only because the gall-bladder has no analogue in the pancreatic duct that the biliary tract is so much more commonly the seat of infection. In this connection we may contrast the infrequency of intrahepatic lithiasis with the infrequency of pancreatic lithiasis: possibly many of the causative factors of both are quite alike. We must also explain why bacteria, innocuous or comparatively innocuous in the intestine, become mischievous immediately they pass the portal of the diverticulum. Possibly the conditions are analogous to those encountered in the vermiform appendix where defective drainage plays such an important etiological role. Finally, it is important to emphasize the fact that were typhoid cholecysstitis, for instance, an ascending infection micro-organisms other than the typhoid bacillus, such as Bacillus coli communis, streptococci, staphylococci, etc., would probably frequently be found in association with the typhoid bacillus, and that the regularity with which the typhoid bacillus is recovered in pure culture from the gall-bladder in typhoid fever renders it unlikely that the infection is an ascending one.

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[1] Quoted by Naunyn, Zur Naturgeschichte der Gallensteine und zur Cholelithiasis, Grenzgeb. der Med. und Chir., 1905, xiv, 537.

In favor of the view that infection may occur by way of the diverticulum of Vater, I may mention that bacteria have been found in the diverticulum under apparently normal conditions; that Lippmann[1] recently has isolated bacteria from the middle and even the upper third of the apparently normal common duct—in numbers decreasing upward; that in the presence of gallstones, bacteria are not infrequently more numerous in the lower end of the common bile duct than elsewhere in the biliary tract; that as we might expect *a priori* motile bacteria, such as Bacillus coli communis, Bacillus typhosus, etc., are much more commonly the invaders than non-motile organisms, such as streptococci, staphylococci, pneumococci, etc.; that experimentally infection has been found to occur with readiness when the flow of the bile has been impeded —in which relation the early experimental work of Gilbert and Girode[2] and others merits attention; and that, finally, I believe significant deductions may be drawn from the recently published and very interesting experiments of Bond[3] on ascending currents in mucous glands and gland ducts. Bond seems to have proved that by some means or other, and under certain conditions, particles of an insoluble substance, such as indigo, inserted into the orifice of a mucous canal or duct are conveyed along the mucous channel in a direction reverse to that taken by the contents of the tube, or by the secretion or excretion of the glands along such ducts —that is, for example, from the duodenum to the gall-bladder, from the urethra to the urinary bladder, etc. Bond believes that this phenomenon is not due to physical agency alone, such as capillary attraction, since it is absent in the non-living tube; and that the transference of the particles in empty tubes and ducts is one, and that there are several other reasons for regarding the mucus that coats the walls of the tube or duct as the vehicle in which the particles are carried. The essential factors seem to be a living tube the walls of which are partially, if not wholly, in apposition and lined with a mucous secretion. Further observation is said to be necessary to ascertain whether a reverse current—a sort of backwater— is present in all mucous channels, or whether it only exists where the normal outgoing current of secretion or excretion is interfered with. Such a back current is probably present to a certain extent normally, although it is much increased by any agency, such as a fistula, which starts a flow of mucus from the other end of the canal.

The application of the foregoing observations to the possibility and the phenomena of ascending infections of the biliary tracts must be quite obvious. Thus, while we cannot deny that infection of the biliary passages may and probably does occur in some cases by way of the diverticulum of Vater, we are forced to the conclusion (1) that certain ill-understood factors exercise in the process a more or less unknown part, and (2) that in the past we have unquestionably overestimated the importance and the significance of this source of infection.

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[1] Loc. cit.

[2] Contribution a l'étude bacteriologique des voies biliaires, Comp. rend. Soc. Biol., 1890, ii, 739.

[3] Ascending Currents in Mucous Glands and Gland Ducts, Brit. Med. Jour., 1905, ii, 232.

2. *Infection by way of the portal circulation* is doubtless a common source of biliary infection, although it was for a long time overlooked. Definite experimental proof that the bile may become infected from the circulation was furnished years ago by Blachstein[1] and Welch,[2] and their results have since been amply confirmed and amplified by a number of investigators, notably Sherrington,[3] Desoubry and Porcher,[4] Nocard,[5] Fütterer,[6] Adami,[7] Ford,[8] Wrzosek,[9] Lartigau,[10] Doerr,[11] and others. Though there have been a few dissenters, such as Carmichael,[12] the recent very accurate studies leave no room for doubt that bacteria transported to the liver by the portal circulation may be found in the bile. Although one may well concede, indeed maintain, that under normal circumstances bacteria carried to the liver by the portal circulation are there destroyed by the bactericidal properties of the liver cells, he must admit a limit to such bactericidal properties and that when overcome bacteria may pass over into the biliary passages. Among others, Lartigau's work is especially conclusive. Having tied the common bile duct in a number of animals he fed the animals Bacillus pyocyaneus, and was subsequently able to recover this organism, sometimes alone, sometimes associated with Bacillus coli communis, from the gall-bladder of almost one-half the animals. Adami having shown that, under apparently normal conditions, bacteria may be found in the deeper layers of the intestine, in the portal circulation, and in the liver, suggests that they invade the

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[1] Intravenous Inoculation of Rabbits with the *Bacillus coli communis* and the Bacillus typhi abdominalis, Johns Hopkins Hosp. Bull., 1891, ii, 96.

[2] Additional Note Concerning the Intravenous Inoculation of the Bacillus typhi abdominalis, Johns Hopkins Hosp. Bull., 1891, ii, 121.

[3] Experiments on the Escape of Bacteria with the Secretions, Jour. Path. and Bact., 1892–93, i, 258.

[4] De la presence de microbes dans le chyle normal chez le chein, Compt. rend. Soc. Biol., 1895, ii, 101.

[5] Influence des repas sur la penetration des microbes dans le sang, Sem. méd., 1895, xv, 63.

[6] Wie bald gelangen Bacterien welche in die Portalvene eingedrungen sind in den grossen Kreislauf und wann beginnt ihre Ausscheidung durch die Leber und die Niere, Berl. klin. Woch., 1899, xxxvi, 58.

[7] On Latent Infection and Subinfection, Jour. Amer. Med. Assoc., 1899, xxxiii, 1509, 1572.

[8] Bacteriology of Healthy Organs, Trans. Assoc. Amer. Phys., 1900, xv, 389.

[9] Experimentelle Beiträge zur Lehre von dem latenten Mikrobismus, Virchow's Archiv, 1904, clxxviii, 82.

[10] The Relation of Bacteria to the Development of Gallstones, California State Jour. of Med., 1906, iv, 17.

[11] Experimentelle Untersuchüngen über das Fortwuchern von Typhusbacillen in der Gallenblase, Centralbl. für Bakt., 1905, xxxix, 624; Wien. klin. Woch., 1905, xviii, 884.

[12] The Effect of Injection of Micro-organisms into the Portal System on the Sterility of the Bile in the Gall-bladder, Jour. Path. and Bact., 1902–03, viii, 276.

portal circulation through the aid of the leukocytes—which are especially active during digestion, carrying foodstuffs, foreign matters, bacteria, etc., between the epithelial cells to the lymphatic radicles and the portal venules. Ordinarily most of the bacteria are destroyed, probably in large part through the bactericidal property of the normal living intestinal mucosa, as maintained by Rolly and Liebermeister,[1] in part also by the leukocytes, the lymph nodes, and the endothelium of the liver; sometimes, however, they pass through the liver and gain the bile; in other cases, by way of the thoracic duct, as maintained by Wrzosek and others, they invade the general circulation, and, as well pointed out by Ford, may be found in the liver, kidneys, etc., of apparently normal animals. This is the latent infection of Adami and certain French and German writers. Recently, Nicholls[2] has described what he designates a simple method of demonstrating the presence of bacteria in the mesentery of normal animals—a method based upon histological procedures, and which, although suggestive, lacks the trustworthiness accorded to cultural methods.

3. *Infection by way of the systemic circulation,* although possibly not an exceedingly common source of infection of the biliary tract, should not be entirely ignored. Its importance as a possible source of infection has been enhanced since we have ascertained the frequency, in fact almost the regularity, of bacteremia in the great majority of infectious processes—typhoid fever, pneumococcic and pyococcic infections, etc.; and experimental proof that the biliary passages may become thus infected was furnished, as already mentioned, years ago by Welch and Blachstein, and quite recently by Doerr. Doerr found that micro-organisms injected into the general circulation of rabbits appear in the gall-bladder within a few hours, and that typhoid bacilli and colon bacilli multiply in the gall-bladder and may be recovered therefrom in pure culture even after the lapse of four months. The resulting lesions were usually catarrhal, but they might become purulent. On the contrary, organisms introduced subcutaneously or intraperitoneally did not lead to infection of the gall-bladder. The occurrence of cholecystitis and cholangitis as a complication of general infections, such as influenza, pneumonia (recently reported upon by Richardson,[3] Anders,[4] etc., and studied experimentally by Brion and Kayser),[5] etc., also suggests the likelihood of the infection occurring by way of the general circulation; but one must concede the possibility

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[1] Experimentelle Untersuchungen über die Ursachen der Abtötung von Bakterien im Dünndarm, Deut. Arch. f. klin. Med., 1905, lxxxiii, 413.

[2] A Simple Method of Demonstrating the Presence of Bacteria in the Mesentery of Normal Animals, Jour. Med. Research, 1904, xi, 455.

[3] Acute Inflammation of the Gall-bladder, AMER. JOUR. MED. SCI., 1898, cxv, 629.

[4] Cholecystitis as a Complication of Croupous Pneumonia, Amer. Med., 1904, ix, 431.

[5] Kunstliche Infektion der Gallenblase mit Pneumokokken nach Choledochusresektion, Grenzgeb. der Med. und Chir., 1903, xii, 677.

of the local biliary infection being due to organisms other than those occasioning the primary infection, and that the complicating infection may occur by way of the portal circulation or the diverticulum of Vater. Infection by way of the hepatic artery is a descending infection and operates as does infection carried by the portal circulation—since both circulations commingle at the periphery of the liver lobules; but infected blood carried by the cystic artery may, although probably rarely, lead directly to infection of the gall-bladder without the intermediation of infected bile.

4. *Infection by way of the lymphatic circulation* has been suggested by G. P. Müller,[1] who, pointing out its likely mechanism, reports a case that he believes illustrates this manner of infection. I am inclined to agree with him, although this is probably a most infrequent source of infection.

5. *Direct infection through the wall of the gall-bladder* or of the ducts from the peritoneum has been suggested as a possibility; but excluding cases of general peritonitis in which the gall-bladder may participate secondarily in the more widespread lesions and in which the mechanism of the local infection may be quite obvious, it is doubtful if infection of the biliary tract directly from the peritoneum can occur in the absence of adhesions—in which event it is probably an infection by way of the lymphatic circulation. In this connection, however, we must also bear in mind that the adhesions themselves are an evidence of past infection, and that an obvious infection in the presence of old adhesions is much more likely the relighting of an old, latent infection, rather than a new infection transmitted directly through the walls of the gall-bladder or the gall ducts.

The pathways of biliary infection doubtless vary with the infecting agent. Bacillus coli infections, which must be looked upon as the most common, doubtless occur most frequently by way of the portal circulation. In most cases the liver in full functional activity is enabled to destroy or render innocuous such colon bacilli as may pass the barrier of the intestinal mucosa and be transported to it; but should the physiological activity of the liver become impaired, or should the colon bacilli become of heightened virulence, as happens in inflammatory and ulcerative processes of the intestine, bacilli of attenuated virulence may pass over into the biliary circulation and, being excreted with the bile, set up a low grade biliary catarrh. This commonly passes unnoticed by the patient, but it is one of the most important factors in the etiology of gallstones, as it is also the most important factor in the complications of gallstones. We must admit, however, that in the event of gastroduodenitis colon bacilli may infect the biliary passages by way of the diverticulum of Vater and the common duct; in this event, the lesions are likely to be more abrupt in onset and more manifest clinically.

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[1] The Pathology of Cholecystitis, Brooklyn Med. Jour., 1905, xix, 11.

Typhoid infection may occur by way of the portal circulation, by way of the systemic circulation, and by way of the diverticulum of Vater. I am inclined to believe that the frequency of gall-bladder infection in typhoid fever finds one of its explanations in the three sources whereby the biliary tract may become infected—although the systemic and the portal circulations are the more important.

Pneumococcic, pyococcic, influenzal infections, etc., are doubtless in many cases general systemic infections; in some cases the infection is probably by way of the diverticulum of Vater—but the subject still requires considerable elucidation.

THE RESULTS OF BILIARY INFECTION. The results of biliary infection vary with the virulence of the infecting micro-organism and the resistance offered by the subject; they may be insidious or frank in onset, acute, subacute, or chronic in course, and slight or extremely severe in character. The frank acute cholangitis and cholecystitis are usually so obtrusive in their manifestations as scarcely to escape observation; and although they sometimes present diagnostic difficulties these are usually overcome with care and the disease is correctly recognized. When, however, the infection is more insidious in onset and subacute or chronic in course and the infecting micro-organisms of low virulence, the resulting lesions are of such nature and the symptoms so slight or altogether absent that they are often ill-understood, misinterpreted, and referred to organs other than their real source.

Since it is manifestly impossible, even if it were desirable (which on this occasion it is not), to review in detail the manifold phenomena of infections of the biliary tract, I have elected to ask your attention to several of the most interesting aspects of the subject only; that is, latent or masked infections, of which many of the typhoid (and paratyphoid) infections serve as a type.

LATENT OR MASKED INFECTIONS.

The introduction of micro-organisms of low virulence into the biliary tract may be unattended by pathological lesions, and this is the more likely to be the case if the ducts are patent and the flow of bile unobstructed. Comparatively virulent micro-organisms also may sometimes be disposed of, if the biliary drainage is free and unimpeded, but usually serious and even fatal forms of disease are thus provoked—suppurative cholangitis and suppurative and gangrenous cholecystitis. Between the extremes of innocuousness or comparative innocuousness and quick and early disaster lie the great majority of cases of biliary infection.

As in other mucous canals, the immediate result of infection of the biliary tract is the production of a catarrh, with the usual inflammatory phenomena—œdema and congestion of the mucous membrane, increased production of mucus, and desquamation of epithelium. If the biliary circulation is free and unimpeded the results of this catarrh are washed away for the most part, but on account of special local conditions (largely dynamic) they are likely to accumulate, to become accentuated, and to persist in the gall-bladder. In the event of obstruction to the free flow of bile these are all the more certain to occur. In many cases the lesions thus provoked are entirely latent or unannounced by noteworthy or unequivocal symptoms; they may pursue a short course, or they may continue for years; and they are one of the most important factors, in fact, the important factor, in the etiology of gallstones. These latent or masked infections are doubtless due to different micro-organisms in different cases, but since a large majority of them are due to the typhoid bacillus (and its brother the paratyphoid bacillus) they may be studied from the point of view of typhoid infections.

TYPHOID INFECTIONS.

Although biliary complications of typhoid fever were by no means unknown to our forefathers, having been noted even by Louis in 1838 and by Murchison in 1862, the noteworthy additions to our knowledge of the subject are of quite recent date. The early history of the development of our knowledge was well reviewed in 1897, by Mason,[1] who collected 14 cases; in 1897, by Osler;[2] in 1898, by Da Costa,[3] who collected 58 cases; and in 1899, by Camac,[4] who collected 115 cases. Since then the subject has been studied by a large number of investigators, and we now have comparative unanimity regarding the following points: (1) That the typhoid bacillus is regularly present in the gall-bladder, and commonly in pure culture, in practically all cases of typhoid fever—indeed, it is the one region of the body from which a pure culture of the organism is most likely to be obtained; (2) that the typhoid bacillus may persist in the gall-bladder, as well as within gallstones, weeks, months, even years, after the patient has recovered from an attack of typhoid fever; (3) that cholangitis and cholecystitis (catarrhal, suppurative, and gangrenous) are by no means infrequent complications of typhoid fever; and (4) that a history of antecedent typhoid fever may be obtained in many cholelithitic and cholecystitic subjects. Furthermore, it is important to bear in mind, as has recently been insisted upon by Doerr,[1] Forster and Kayser,[2] Brion and Kayser,[3] and as is suggested also by my own studies, that many of these subjects—some apparently healthy and others ill only with a local disorder—are unconscious harborers and disseminators of the typhoid bacillus. The continuous reinfection of the intestinal tract by the frequent discharge of virulent typhoid bacilli from a chronically infected gall-bladder may be of much significance to the individual, but it is of even more significance from an epidemiological point of view—since there can be little doubt that these apparently healthy harborers of typhoid bacilli spread the infection and sometimes may even give rise to more or less extensive epidemics.

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[1] Gall-bladder Infection in Typhoid Fever, Trans. Assoc. Amer. Phys., 1897, xii, 23.

[2] Hepatic Complications of Typhoid Fever, Trans. Assoc. Amer. Phys., 1897, xii, 378.

[3] Significance of Jaundice in Typhoid Fever, AMER. JOUR. MED. SCI., 1898, cxvi, 1; Cases of Typhoid Cholecystitis Ending in Recovery, ibid., 1899, cxviii, 138.

[4] Cholecystitis Complicating Typhoid Fever, AMER. JOUR. MED. SCI., 1899, cxvii, 275; Gall-bladder Complications of Typhoid Fever, Johns Hopkins Hosp. Reports, 1899–1900, viii, 339.

If, in some cases, the typhoid bacillus is present in the gall-bladder without exciting pathological lesions, in many cases lesions are produced; all degrees are encountered—from the mild catarrh to the severest suppurative and gangrenous processes with perforation of the gall-bladder. What I desire to emphasize, however, is the fact that in many cases the biliary infection though present is altogether latent clinically, and that although in other cases it occasions demonstrable symptoms, the true nature of these is often masked and they escape correct interpretation. First, there are cases in which during the course of typhoid fever a noteworthy enlargement of the gall-bladder occurs; but the biliary ducts being patent, and the drainage therefore sufficient, and the patient's sensibilities somewhat obtunded, there is no complaint and the disorder escapes clinical recognition—unless perchance systematic and repeated examinations of the gall-bladder region are undertaken; in this event a more or less enlarged and tender gall-bladder may be encountered. I believe that it is really surprising how frequently this occurs; shall I also say surprising how frequently it goes undetected? Second, there are cases in which a little epigastric discomfort, perhaps slight nausea, in some cases actual pain, is complained of, and examination reveals an enlarged and tender gall-bladder. I have come to regard nausea during the course of typhoid fever, when not due to other obvious cause, as quite significant of gall-bladder infection, although, of course, it may be due to other factors. Third, there are cases in which announced by the ordinary symptoms an acute cholecystitis or cholangitis develops —often severe in type. This is probably more common during or after convalescence than during the course of the infection. Such is often the severity of the symptoms in these cases that I invite a surgeon to see the patient with me: his advice is always valuable, and although the infection commonly subsides spontaneously, an operation may be called for at any time—in which event it is desirable that the surgeon should have had an opportunity to watch the progress of the disorder.

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[1] Loc. cit.

[2] Ueber das Vorkommen von Typhusbazillen in der Galle von Typhuskranken und "Typhus bazillenträgern," Münch. med. Woch., 1905, lii, 1473.

[3] Neuere Klinisch-bacteriologische Erfahrungen bei Typhus und Paratyphus, Deut. Archiv. f. klin. Med., 1906, lxxxv, 525.

There are, in addition, several other aspects of typhoid infection of the biliary tract worthy of study:

RELAPSE IN TYPHOID FEVER. First of all, I must point out the significant fact, first insisted upon I believe by Musser, that in reality many of the so-called relapses in typhoid fever are by no means relapses in a restricted sense, but rather manifestations of some local infection of the body—often of the biliary tract, cholecystitis. The more attentively I study my typhoid fever patients the less inclined I am to pass by a so-called relapse as a relapse only; in fact, I feel somewhat chagrined if I am unable to put my finger upon some definite cause for the return of the fever. In many cases a gall-bladder infection will be found; in other cases, an infection of the urinary tract; in others, fecal impaction, furunculosis, osteitis, periostitis, etc., while in still other cases the increased flow of infected bile occasioned by a return to a liberal diet, or other factors, may determine what may be looked upon as a real relapse—commonly reinfection from an infected gall-bladder. But in most cases, persistent search for a definite local infection will be rewarded with success. These, especially the gall-bladder infections, have important surgical bearings, and should be attentively studied. It is true that the inflammatory phenomena frequently subside spontaneously and the indication for the surgical intervention passes away; but these infections are a fruitful source of mischief in later life—often causing gallstones, subacute and chronic cholecystitis, pericholecystic adhesions, and divers other ills that commonly are grouped with the congeries of symptoms designated "stomach trouble."

PRIMARY TYPHOID CHOLECYSTITIS. Then I must ask your attention to the occurrence of a primary typhoid cholecystitis and cholangitis—an infection of the biliary tract without other evidence of past or present typhoid infection. My attention was directed to this subject in 1901, by Pratt,[1] who, reporting two cases, referred to three other cases in the literature (Cushing, Mitchell, and Hunner). Since then the subject has been studied by Stockton and Lytle,[2] Burlew,[3] Stewart,[4] Rudolph Müller,[5] Doerr,[6] Forster and Kayser,[7] Blumenthal,[8] Findlay and Buchanan,[9] etc.

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[1] Typhoid Cholecystitis, AMER. JOUR. MED. SCI., 1901, cxxii, 584.

[2] New York State Med. Jour., 1902, ii, 232.

[3] Typhoid Cholecystitis and Calculi without any Evidence of Typhoid Fever, Medicine, 1903, ix, 734.

[4] Primary Typhoid Cholecystitis, Amer. Med. 1904, vii, 1018.

[5] Cholecystitis und Cholangitis als Ursache von positiver Gruber-Widalscher Reaktion bei Ikterus, Zeit. f. Heilk., path. Anat. Heft, 1905, xxvi, 263.

[6] Loc. cit.

[7] Loc. cit.

[8] Ueber das Vorkommen von Typhus- und Paratyphusbazillen bei Erkrankungen der Gallenwege, Münch. med. Woch., 1904, xxxvii.

[9] A Case of Typhoidal Cholecystitis, Glasgow Med. Jour., 1906, lxv, 177.

The typhoid bacillus[1] was isolated from the gall-bladder of 7 of Dr. Deaver's 216 patients; and from the gall-bladder of another patient operated upon in 1906.[2] All of these 8 patients were women. In 4 no history of previous typhoid fever, nor of concurrent typhoid fever (in the commonly accepted sense), could be obtained.

The first patient, K. H., aged forty-nine years, was admitted to the hospital June 22, 1903. The first attack of pain occurred ten years prior to admission, and the pain recurred about twice a year thereafter. Operation revealed the gall-bladder thickened and contracted, extensive adhesions between the gall-bladder, the duodenum, and the stomach, a cholecystogastric fistula, and many gallstones in the adhesions. Cholecystectomy was done, and the patient recovered.

The second patient, K. C., aged fifty-six years, was admitted to the hospital August 24, 1903. The first attack of pain occurred four years prior to admission; recurrences were frequent. Operation revealed the gall-bladder enlarged, necrotic, and ulcerated, about fifty gallstones and 150 c.c. of pale, yellowish pus in the gall-bladder, and many adhesions between the gall-bladder, the duodenum, and the stomach. Cholecystectomy was done, and the patient recovered.

The third patient, E. H., aged twenty-seven years, was admitted to the hospital March 11, 1904. The first attack of pain occurred three weeks prior to admission. Operation revealed suppurative cholecystitis, about 100 c.c. of yellowish purulent material in the gall-bladder, one gallstone obstructing the cystic duct, and adhesions between the gall-bladder, the liver, the duodenum, and the omentum. Cholecystectomy was done, and the patient recovered.

The fourth patient, A. C., aged forty-seven years, was admitted to the hospital April 27, 1904. The first attack of pain occurred two years prior to admission; recurrences were frequent. Operation revealed suppurative cholecystitis, many stones, and about 100 c.c. of bloody, yellowish, purulent fluid in the gall-bladder, and a few pericystic adhesions. Cholecystectomy was done and the patient recovered.

The fifth patient, S. W., aged fifty-six years, was admitted to the hospital June 22, 1903. Nine weeks prior to admission the patient was taken ill with what was said to have been typhoid fever—chills, fever, anorexia, headache, vomiting, etc. Four weeks later pain in the gall-bladder region was complained of and a mass was detected. Operation revealed the gall-bladder enlarged, necrotic, ulcerated, and perforated; it contained one stone and a considerable amount of dark, purulent bile. There were many adhesions between the gall-bladder, the pylorus, the duodenum, the colon, and the omentum. Cholecystostomy with drainage was done, and the patient recovered.

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[1] The following biological characteristics of an organism under investigation were looked upon as proof of its being the typhoid bacillus: An actively motile bacillus that grew well on all the ordinary laboratory media; a delicate, translucent, slightly bluish, or iridescent growth with irregular or serrated edges on agar surfaces; a whitish, almost if not quite invisible, growth on potato; no gas production in glucose, saccharose, or levulose media; no indol production; no coagulation and no (or very slight) acidulation of milk; and a positive Gruber-Widal reaction with known typhoid serum in dilutions of 1 to 50 or 1 to 100 or higher.

[2] This patient, of course, had not been observed at the time the Lecture was delivered, but the notes of the case are included here for obvious reasons.

The sixth patient, M. R., aged forty-two years, was admitted to the hospital January 30, 1905. She had had typhoid fever fifteen years previously. The first attack of pain occurred one month after the typhoid fever; recurrences were frequent. Operation revealed a chronic cholecystitis, twenty gallstones in the gall-bladder, one stone in the common duct, and many adhesions between the gall-bladder, the liver, the duodenum, the stomach, and the omentum. Cholecystostomy with drainage was done, and the patient recovered.

The seventh patient, J. Y., aged thirty-eight years, was ill in the German Hospital with typhoid fever from April 25 to May 30, 1905. On June 7th she had what was called indigestion. On June 22d the first definite colic occurred. On July 2d she was readmitted to the hospital. Operation revealed an enlarged gall-bladder with unusually thickened walls (up to 14 mm.), one stone and about 60 c.c. of pus in the gall-bladder, and many adhesions between the gall-bladder, the edge of the liver, and the omentum. Cholecystostomy with drainage was done and the patient recovered.

The eighth patient, P. E., aged forty years, was admitted to the Hospital July 2, 1906. She had had typhoid fever fourteen years previously, and subsequently has suffered repeatedly from "stomach trouble." The first definite gallstone colic occurred eleven days prior to admission to the hospital; there were two subsequent colics. Operation revealed the gall-bladder enlarged, thickened, and congested; its mucous membrane was completely necrotic, detached, forming a veritable cast; and there were fifty to seventy gallstones in the gall-bladder. Cholecystectomy was done and the patient recovered. On August 4, 1906 (after convalescence), the patient's blood yielded a positive Gruber-Widal reaction with the typhoid bacillus.

In addition to these eight patients from whose gall-bladders the typhoid bacillus was isolated, two other rather interesting patients were observed:

The ninth patient, C. S., a male, aged thirty-five years, was admitted to the hospital March 2, 1905. He had had his first attack of colic four years before admission; a second attack three years before admission; typhoid fever fifteen months before admission; and a third attack of colic three weeks before admission. Operation revealed an enlarged and distended gall-bladder, about 200 c.c. of clear, brownish-green bile in the gall-bladder, three gallstones in the common duct, and no adhesions. Cholecystostomy with drainage was done. The patient had been jaundiced for a long time, and died of capillary oozing and cholemia. His blood serum gave a positive Gruber-Widal reaction with the typhoid bacillus, but the colon bacillus only was isolated from his gall-bladder (at the time of operation).

The tenth patient, M. O., a female, aged fifty-five years, was admitted to the hospital August 11, 1905. She had had typhoid fever seven years prior to admission. The first attack of colic occurred four years prior to admission. Operation revealed a thickened and atrophic gall-bladder, one stone in the gall-bladder, adhesions between the gall-bladder, the liver, the duodenum, and the stomach. Cholecystostomy with drainage was done, and the patient recovered. Her blood serum gave a positive Gruber-Widal reaction with the typhoid bacillus. No cultures were taken.

This primary typhoid cholecystitis is of much importance from several points of view, and heretofore has been insufficiently studied. The first four cases just cited are apparently examples of primary typhoid infection of the biliary tract; the fifth, sixth, seventh, eighth, and tenth cases are obviously examples of a local infection persisting after the general infection had subsided—acute in the fifth and seventh, chronic in the sixth, eighth, and tenth cases. In the sixth case it is not unlikely that the typhoid bacillus was harbored in the gall-bladder for fifteen years—since the first attack of colic occurred one month after an attack of typhoid fever, recurrences of the colic were frequent during the subsequent fifteen years, and the typhoid bacillus was recovered from the gall-bladder at operation. It is not improbable also that the typhoid bacillus was carried in the gall-bladder fourteen years in the eighth patient (the duration of the symptoms designated "stomach trouble"), ten years in the first patient, four years in the second, and two years in the fourth—the duration of the symptoms in the respective patients; but, of course, one cannot exclude the possibility of typhoid infection of an already infected gall-bladder. This is true also of the ninth patient, in whom it is furthermore interesting to speculate whether or not the attack of typhoid fever was precipitated by infection from a chronically infected gall-bladder. The isolation of the colon bacillus only from the gall-bladder in this patient suggests the probability of subsequent Bacillus coli infection of the gall-bladder.

These cases of apparently long-standing typhoid infection of the gall-bladder recall several similar observations recorded in the literature; for instance, the case reported by Ramond and Faitout,[1] in which the typhoid bacillus was recovered from the gall-bladder six years after an attack of typhoid fever; Miller's[2] case, after seven years; von Dungern's[1] case, after fourteen years; Droba's[2] case, after seventeen years; Hunner's[3] case, after eighteen years; and Camac's[4] case, after twenty years. These cases serve also to emphasize the epidemiological significance of these unconscious carriers of typhoid bacilli—to which I have already alluded. Doubtless bacteriological investigation of the stools of chronic cholecystitic subjects would perhaps frequently disclose the typhoid bacillus. An interesting feature of many of the typhoid infections of the biliary tract is the seriousness of the lesions—well exemplified in the cases herewith reported.

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[1] Angiocholecystite a bacille d'Eberth, Comp. rend. Soc. Biol., 1896, iii, 1130.

[2] The Presence of Bacillus Typhosus in the Gall-bladder Seven Years after Typhoid Fever, Johns Hopkins Hosp. Bull., 1898, ix, 95.

THE GRUBER-WIDAL REACTION IN CASES OF JAUNDICE. Since the earliest days of the clinical use of the Gruber-Widal reaction in the diagnosis of typhoid fever, cases of so-called catarrhal (as well as other forms of) jaundice have been observed in which the serum reaction was positive—whence at first it was not unnaturally thought that possibly jaundice vitiated the diagnostic trustworthiness of the serum reaction. However, since we have come to recognize the importance and the frequency of typhoid infection of the biliary tract, since we have learned of the occurrence of a primary typhoid cholecystitis and cholangitis, we have come also to think that these cases of jaundice are examples of typhoid infection, and that the Gruber-Widal reaction is of much importance in determining the nature of the jaundice (infection). This question has been studied attentively recently by Zupnik,[5] Eckardt,[6] Königstein,[7] Libman,[8] Zevi,[9] Rudolph Müller,[10] Ludke,[11] Steinberg,[12] Blumenthal,[13] Netter and Ribadeau-Dumas,[14] Brion and Kayser,[15] etc.

In a number of cases of jaundice that have yielded a positive Gruber-Widal reaction the typhoid bacillus has been isolated from the biliary tract—at operation or after death; and since it has been determined experimentally that the bile as such has little if any tendency to cause agglutination of the typhoid bacillus, it is only reasonable to look upon a positive serum reaction in cases of jaundice as evidence of typhoid infection of the biliary tract. Heretofore, for obvious reasons, we have had to be content with a diagnosis of cholecystitis and cholangitis; a noteworthy advance in our diagnosis would be the recognition of the etiological agent. When cholecystitis or cholangitis complicates pneumonia, influenza, typhoid fever, dysentery, etc., the natural inference is that the primary infective agent is the cause of the complication—an inference usually but not always borne out by the fact. When, however, the cholecystitis of cholangitis occurs independently of any manifest general infection, when other evidence of general or local infection cannot be detected, the recognition of the nature of the local biliary infection is beset with difficulties.

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[1] Ueber Cholecystitis typhosa, Münch. med. Woch., 1897, xliv, 699.

[2] Der Zusammenhang zwischen Typhusinfektion und Cholelithiasis, Wien. med. Woch. 1899, xii, 1141.

[3] A Case of Acute Suppurative Cholecystitis with Isolation of the Bacillus Typhosus Eighteen Years after an Attack of Typhoid Fever, Johns Hopkins Hosp. Bull., 1899, x, 163.

[4] Gall-bladder Complications of Typhoid Fever, Johns Hopkins Hosp. Reports, 1899–1900, viii, 353.

[5] Erfahrungen über die Gruber-Widal'sche Reaktion und Autoagglutination bei Typhus abdominalis, Ztsch. f. Heil., path. Anat. Heft, 1901, xxii, 334.

[6] Widal'sche Serumreaktion bei Weil'scher Krankheit, Münch. med. Woch., 1902, xlix, 1129.

[7] Ueber die agglutinierende Eigenschaft der Galle und des Serums beim Ikterus, Wien. klin. Woch., 1903, xvi, 985.

[8] Notes on the Widal Reaction, Med. News, 1904, lxxxiv, 204.

[9] Ueber die Gruber-Widal'sche Reaktion bei Ikterus, Wien. klin. Woch., 1904, xvii, 861.

[10] Loc. cit.

[11] Agglutination bei Autoinfektionen mit besonderer Berücksichtigung des Ikterus, Deut. Archiv. f. klin. Med., 1904, lxxxi, 34.

[12] Ueber Agglutination von Typhusbazillen durch das Blutserum Ikterischer, Münch. med. Woch., 1904, li, 469.

[13] Ueber die Bedeutung der Gruber-Widal'schen Reaktion bei Erkrankungen der Leber und der Gallenwege, Medizinische Klinik, 1905, i, 1227 (other ref.).

[14] Details sur l'agglutination dans trente-sept cas de typhoides and paratyphoides. Compt. rend. Soc. Biol., 1905, xlix. 373. (Other articles in the same volume.)

[15] Loc. cit.

There can be little doubt that we have much to learn of the nature of certain ill-understood forms of jaundice—so-called febrile jaundice, infectious jaundice, Weil's disease, etc. The resemblance that many of these cases bear to typhoid fever has been frequently commented upon, and it has in fact been suggested that Weil's disease is in reality a modified form of typhoid fever. Possibly in many cases it is only typhoid infection of the biliary tract. That this may well be so is suggested by the extreme variability of the known lesions of typhoid infection of the biliary tract—from the mildest local catarrhal lesions to widespread and fatal suppurative cholecystitis, cholangitis, and multiple abscesses of the liver. Furthermore, it is interesting to bear in mind that jaundice sometimes occurs at the onset of typhoid fever, as in some cases reported by Ogilvie[1] and others, and that epidemics of so-called catarrhal jaundice are occasionally observed. Dalgeish,[2] for instance, has reported such an epidemic that occurred in Bloemfontein, which he says resembled in many respects the prevailing typhoid fever and was thought to be due to the typhoid bacillus.

It would be wise, therefore, in all cases of jaundice to undertake bacteriological studies of the blood and the feces; whether or not these be feasible, the Gruber-Widal reaction with the typhoid, paratyphoid, and other bacilli should not be neglected. I should be inclined to consider a positive reaction in a dilution of 1 to 50 or 1 to 100, or higher, conclusive evidence of typhoid infection, having in mind, of course, the possibility of previous typhoid fever. In some reported cases positive reactions have been obtained at much higher dilutions—1 to 1800 (Rudolph Müller) and higher.

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[1] Jaundice in Typhoid Fever, Brit. Med. Jour., 1901, i, 75.

[2] An Epidemic of Catarrhal Jaundice Probably due to the Enteric Fever Bacillus, Lancet 1901, ii, 523.